Aflibercept 8 mg monotherapy shows maintained efficacy over 96 weeks, with the ability to extend dosing intervals beyond every 16 weeks, in patients with PCV in the PULSAR Phase 3 trial

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PURPOSE

This subgroup analysis of the PULSAR Phase 3 trial evaluated the efficacy and safety of aflibercept 8 mg monotherapy in patients with treatment-naïve polypoidal choroidal vasculopathy (PCV) over 96 weeks.

METHODS

PULSAR (NCT04423718) was a double-masked, 96-week, Phase 3 trial in patients aged ≥50 years with treatment-naïve neovascular age-related macular degeneration (nAMD). Patients were randomly assigned 1:1:1 to receive intravitreal aflibercept 8 mg every 12 or 16 weeks (8q12 or 8q16) or 2 mg every 8 weeks (2q8), each after 3 initial monthly injections (**Figure 1**). The dosing regimens in the 8q12 and 8q16 groups could be shortened from Week 16 and extended from Week 52 based on predefined protocol criteria. This subgroup analysis focused on patients with PCV, as confirmed by indocyanine green angiography (ICGA), at a central reading center. Subgroup analyses were exploratory only.

FIGURE 1:
PULSAR: Dosing schedule and regimen modification in Years 1 and 2

	YEAR 1															YEAR 2												
	Day 1	Week 4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96
2q8	X	X	X		X	o	X	o	X	o	X	o	X	o	X	o	X	o	X	o	X	o	X	o	–
8q12	X	X	X		o[a]	X[a]	o	o	X[a]	o	o	X[a]	o	o	X[a,b]	o	o	X[a,b]	o	o	X[a,b]	o	o	X[a,b]	–
8q16	X	X	X		o[a]	o[a]	X[a]	o	o	o	X[a]	o	o	o	X[a,b]	o	o	o	X[a,b]	o	o	o	X[a,b]	o	–

[a]DRM: Interval shortening during Years 1 and 2

Criteria for interval shortening
- >5-letter loss in BCVA compared with Week 12 due to persistent or worsening nAMD **AND**
- >25 µm increase in CRT compared with Week 12, **OR** new foveal neovascularization, **OR** new foveal hemorrhage

- Patients who met DRM criteria had dosing intervals shortened to q8 at **Weeks 16** and **20** or by 4-week increments from **Week 24**
  - The minimum assigned dosing interval was q8

[b]DRM: Interval extension during Year 2

Criteria for interval extension
- <5-letter loss in BCVA compared with Week 12 **AND**
- No fluid at the central subfield on OCT **AND**
- No new foveal hemorrhage or foveal neovascularization

- Patients who met DRM criteria from **Weeks 52 through 96** had dosing intervals extended by 4-week increments
  - The maximum assigned dosing interval was q24

Figure does not reflect all dosing options once a patient's dosing interval is shortened or extended. Stippled boxes = initial treatment phase; X = active injection; o = sham injections. **q8**, every 8 weeks; **q24**, every 24 weeks; **BCVA**, best-corrected visual acuity; **CRT**, central retinal subfield thickness; **DRM**, dose regimen modification; **OCT**, optical coherence tomography.

RESULTS

PULSAR was conducted across 27 countries. ICGA assessments were optional and were conducted in 13 of these countries. PCV was confirmed to be present in 139 of the 296 patients with ICGA results (2q8: n=54; 8q12: n=44; 8q16: n=41); PCV could not be graded in 3 patients. The majority of patients were Asian (69.8%), and 29.5% were White. The baseline demographics and disease characteristics of the PULSAR subgroup (**Table 1**) were similar to those of the overall PULSAR population (data not shown).

RESULTS cont'd

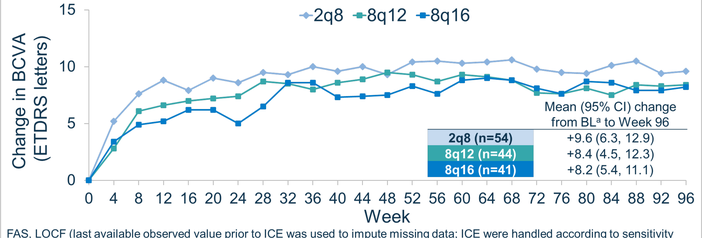
TABLE 1:
Baseline demographics and disease characteristics

	2q8 (n=54)	8q12 (n=44)	8q16 (n=41)	All 8 mg (n=85)
Age, years	72.6 ±8.2	72.2 ±8.1	73.2 ±8.7	72.7 ±8.3
Female, n (%)	17 (32)	22 (50)	15 (37)	37 (44)
Race, n (%)[a]				
Asian	40 (74)	29 (66)	28 (68)	57 (67)
White	14 (26)	14 (32)	13 (32)	27 (32)
Not reported	0	1 (2)	0	1 (1)
BCVA, ETDRS letters	57.6 ±15.5	56.3 ±13.3	60.1 ±11.5	58.1 ±12.5
CRT, µm	378 ±163	392 ±129	377 ±139	384 ±134
CNV size, mm²	5.8 ±4.7	5.1 ±3.8	5.2 ±4.5	5.1 ±4.2

FAS. Data are mean ±SD unless otherwise indicated. ICGA images were graded by the reading center. [a]No patients were reported as being Black or African American, or multi-racial. **BCVA**, best-corrected visual acuity; **CNV**, choroidal neovascularization; **ETDRS**, Early Treatment Diabetic Retinopathy Study; **FAS**, full analysis set.

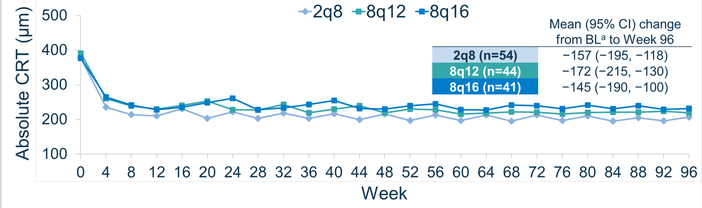
In the PCV subgroup, all 3 treatment arms reported similar BCVA gains (**Figure 2**) and decreases in absolute CRT through Week 96 (**Figure 3**). The gains in BCVA through Week 96 were numerically higher in the PCV subgroup than in the overall PULSAR population (data not shown).

FIGURE 2:
Change in BCVA from baseline through Week 96



FAS, LOCF (last available observed value prior to ICE was used to impute missing data; ICE were handled according to sensitivity estimand strategy for continuous endpoints). N values are the number of patients with BCVA assessments at baseline. [a]Baseline BCVA for 8q12, 8q16, and 2q8 was 56.3±13.3, 60.0±11.5, and 57.6±15.4 letters, respectively. **BL**, baseline; **ICE**, intercurrent events; **LOCF**, last observation carried forward.

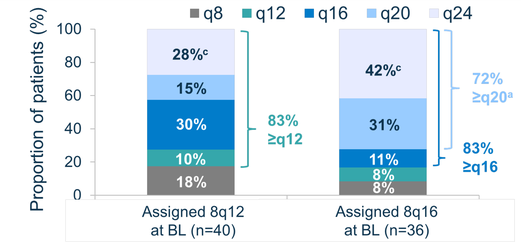
FIGURE 3:
Absolute CRT from baseline through Week 96



FAS, LOCF (last available observed value prior to ICE was used to impute missing data; ICE were handled according to sensitivity estimand strategy for continuous endpoints). N values are the number of patients with CRT assessments at baseline. [a]Baseline CRT for 8q12, 8q16, and 2q8 was 392±130, 377±140, and 378±163 µm, respectively.

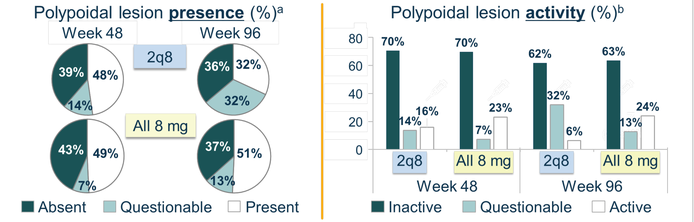
The aflibercept 2 mg and 8 mg groups received a mean total of 12.7 and 8.7 injections from baseline to Week 96, respectively. At Week 96, 83% of patients in each of the 8q12 and 8q16 arms had a last assigned dosing interval of ≥12 weeks and ≥16 weeks, respectively (**Figure 4**). Aflibercept 8 mg markedly reduced the total area of polypoidal lesions from screening to Week 96 (0.15 mm² vs. 0.07 mm²), as well as the proportion of patients with any polypoidal lesions or active polypoidal lesions (**Figure 5**).

FIGURE 4:
Last assigned dosing interval at Week 96



Data are for patients who completed Week 96. Values may not add up to 100% due to rounding. [a]Patients assigned to a 24-week dosing interval did not have enough time to complete the interval within the 96-week study period. **q12**, every 12 weeks; **q16**, every 16 weeks; **q20**, every 20 weeks.

FIGURE 5:
Status of polypoidal lesions



All data are for patients who completed W96: 2q8, n=49; All 8 mg, n=76. Percentages calculated based on number of patients who underwent assessment. [a]W48, n=44 (2q8) and n=69 (All 8 mg); at W96, n=47 (2q8) and n=71 (All 8 mg). [b]W48, n=44 (2q8) and n=69 (All 8 mg); at W96, n=47 (2q8) and n=71 (All 8 mg); patients with inactive polypoidal lesions were defined as those with no polypoidal lesions present OR patients with polypoidal lesions present but both IRF and SRF known to be absent. **IRF**, intraretinal fluid; **SRF**, subretinal fluid; **W**, week.

The safety profile of aflibercept 8 mg and 2 mg was similar in the PCV subgroup (**Table 2**) and overall PULSAR population (data not shown). There were no new safety signals in patients with PCV.

TABLE 2:
Ocular TEAEs in the study eye

TEAE, n (%)	2q8 (n=54)	8q12 (n=44)	8q16 (n=41)	All 8 mg (n=85)
Any ocular TEAE	21 (38.9)	20 (45.5)	20 (48.8)	40 (47.1)
Any intraocular inflammation TEAE	1 (1.9)	1 (2.3)	0	1 (1.2)

Data are from the SAF. TEAEs are adverse events occurring from the first injection to 30 days after the last injection (active or sham); ocular TEAEs are those occurring in the study eye. **TEAE,** treatment-emergent adverse event; **SAF,** safety analysis set.

CONCLUSIONS

Aflibercept 8 mg (8q12 and 8q16) provided similar improvements in BCVA in patients with PCV compared with aflibercept 2 mg given every 8 weeks.

BCVA gains observed with aflibercept 8 mg monotherapy were largely maintained over 96 weeks, with the ability to extend treatment intervals in patients with PCV.

Aflibercept 8 mg and 2 mg treatment led to robust regression in polypoidal lesions through Week 96.

In the PULSAR study, the safety profile of aflibercept 8 mg was similar to that of aflibercept 2 mg in the PCV subgroup and overall study population.

Disclosures

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